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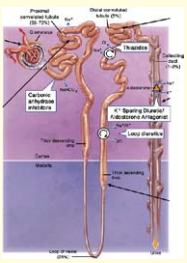
STATE-OF-THE-ART PAPERS



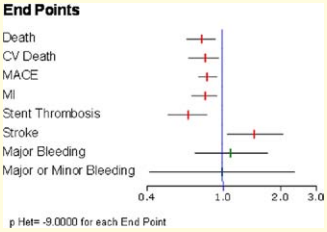
STATE-OF-THE-ART PAPER

A challenging subset of heart failure patients have fluid overload despite large doses of loop diuretics. One approach is to add a thiazide-type diuretic to produce diuretic synergy via "sequential nephron blockade," first described more than 40 years ago. Jentzer and colleagues summarize the existing literature evaluating the combination of loop and thiazide diuretics and find that it has never been subjected to large-scale clinical trials, but it can more than double daily urine sodium excretion. The risks of combination therapy include severe hypokalemia, in addition to hyponatremia, hypotension, and worsening renal function. Considerations about the prudent use of this powerful therapy and a review of potential misconceptions are also provided.

STATE-OF-THE-ART PAPER

Acute aortic syndromes have high mortality without definitive, early treatment. Currently, a high index of clinical suspicion is necessary to divert a patient into a definitive algorithm of imaging studies. A biomarker with high sensitivity would be helpful in guiding more patients to the imaging pathway, but specificity is needed to avoid unnecessary delays in treatments for other conditions. C-reactive protein, D-dimers, soluble elastin fragments, and smooth muscle myosin heavy chain are all potentially useful, and the data regarding their utility are described in this paper by Ranasinghe and Bonser.

CLINICAL RESEARCH



INTERVENTIONAL CARDIOLOGY

Bellemain-Appaix and colleagues performed a meta-analysis to determine if the new $P2Y_{12}$ inhibitors improve clinical outcomes. Data from almost 50,000 subjects were included, with 94% having an acute coronary syndrome and 84% undergoing percutaneous coronary intervention (PCI). New $P2Y_{12}$ inhibitors significantly reduced death (odds ratio: 0.83). In subjects who underwent PCI, new $P2Y_{12}$ inhibitors also significantly reduced major adverse cardiac events and stent thrombosis. While there was an increase in Thrombolysis In Myocardial Infarction major bleeding for "any" PCI, no difference was observed in PCI for ST-segment elevation myocardial infarction (STEMI). After PCI, new $P2Y_{12}$ inhibitors reduce mortality compared with clopidogrel, with a particularly favorable risk/benefit ratio in patients presenting with STEMI.

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CARDIAC GENETICS

Themistocles L. Assimes, Hilma Hólm, Sekar Kathiresan, Muredach P. Reilly, Gudmar Thorleifsson, Benjamin F. Voight, Jeanette Erdmann, Christina Willenborg, Dhananjay Vaidya, Changchun Xie, Chris C. Patterson, Thomas M. Morgan, Mary Susan Burnett, Mingyao Li, Mark A. Hlatky, Joshua W. Knowles, John R. Thompson, Devin Absher, Carlos Iribarren, Alan Go, Stephen P. Fortmann, Stephen Sidney, Neil Risch, Hua Tang, Richard M. Myers, Klaus Berger, Monika Stoll, Svati H. Shah, Gudmundur Thorgeirsson, Karl Andersen, Aki S. Havulinna, J. Enrique Herrera, Nauder Faraday, Yoonhee Kim, Brian G. Kral, Rasika Mathias, Ingo Ruczinski, Bhoom Suktitipat, Alexander F. Wilson, Lisa R. Yanek, Lewis C. Becker, Patrick Linsel-Nitschke, Wolfgang Lieb, Inke R. König, Christian Hengstenberg, Marcus Fischer, Klaus Stark, Wibke Reinhard, Janina Winogradow, Martina Grassl, Anika Grosshennig, Michael Preuss, Stefan Schreiber, H-Erich Wichmann, Christa Meisinger, Jean Yee, Yechiel Friedlander, Ron Do, James B. Meigs, Gordon Williams, David M. Nathan, Calum A. MacRae, Liming Qu, Robert L. Wilensky, William H. Matthai Jr, Atif N. Qasim, Hakon Hakonarson, Augusto D. Pichard, Kenneth M. Kent, Lowell Satler, Joseph M. Lindsay, Ron Waksman, Christopher W. Knouff, Dawn M. Waterworth, Max C. Walker, Vincent E. Mooser, Jaume Marrugat, Gavin Lucas, Isaac Subirana, Joan Sala, Rafael Ramos, Nicola Martinelli, Oliviero Olivieri, Elisabetta Trabetti, Giovanni Malerba, Pier Franco Pignatti, Candace Guiducci, Daniel Mirel, Melissa Parkin, Joel N. Hirschhorn, Rosanna Asselta, Stefano Duga, Kiran Musunuru, Mark J. Daly, Shaun Purcell, Sandra Eifert, Peter S. Braund, Benjamin J. Wright, Anthony J. Balmforth, Stephen G. Ball, Myocardial Infarction Genetics Consortium, Wellcome Trust Case Control Consortium, Cardiogenics, Willem H. Ouwehand, Panos Deloukas, Michael Scholz, Francois Cambien, Andreas Huge, Thomas Scheffold, Veikko Salomaa, Domenico Girelli, Christopher B. Granger, Leena Peltonen, Pascal P. McKeown, David Altshuler, Olle Melander, Joseph M. Devaney, Stephen E. Epstein, Daniel J. Rader, Roberto Elosua, James C. Engert, Sonia S. Anand, Alistair S. Hall, Andreas Ziegler, Christopher J. O'Donnell, John A. Spertus, David Siscovick, Stephen M. Schwartz, Diane Becker, Unnur Thorsteinsdottir, Kari Stefansson, Heribert Schunkert, Nilesh J. Samani, Thomas Quertermous

Recent prospective studies suggest that carriers of the 719Arg allele in kinesin-like protein-6 (KIF6) are at increased risk of clinical coronary artery disease (CAD) compared with noncarriers. Assimes and colleagues sought to confirm this association and genotyped subjects in 19 case-control studies involving over 17,000 cases of CAD and 39,000 controls. None of the 19 studies demonstrated an increased risk of CAD in carriers of the 719Arg allele. Regression analyses and fixed effect meta-analyses ruled out with a high degree of confidence an increase of ≥2% in the risk of CAD with this allele. The KIF6 Trp719Arg polymorphism was not associated with the risk of clinical CAD in this large replication study.

Editorial Comment: Eric J. Topol, Samir B. Damani, p. 1564

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CARDIAC RESYNCHRONIZATION

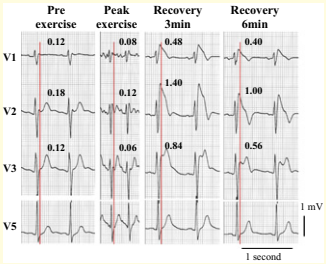
Effect of Biventricular Pacing on Diastolic Dyssynchrony 1567

Miriam Shanks, Matteo Bertini, Victoria Delgado, Arnold C. T. Ng, Gaetano Nucifora, Rutger J. van Bommel, C. Jan Willem Borleffs, Eduard R. Holman, Nico R. L. van de Veire, Martin J. Schalij, Jeroen J. Bax

Shanks and colleagues examined the effect of cardiac resynchronization therapy (CRT) on diastolic dyssynchrony in almost 300 subjects who underwent CRT placement. CRT responders were defined as having ≥15% decrease in left ventricular end-systolic volume at 6 months. At baseline, systolic dyssynchrony was present in 46%, diastolic dyssynchrony in 52%, and both in 29% of subjects. Compared to nonresponders, responders had longer systolic and diastolic delays at baseline. After 6 months, the systolic and diastolic delays improved in CRT responders but did not change in nonresponders. Further studies on the pathophysiology of diastolic dyssynchrony and its changes with CRT appear warranted.

HEART RHYTHM DISORDERS

Post-Exercise ST-Segment Elevation Identifies High-Risk Brugada Patients 1576



Hisaki Makimoto, Eiichiro Nakagawa, Hiroshi Takaki, Yuko Yamada, Hideo Okamura, Takashi Noda, Kazuhiro Satomi, Kazuhiro Suyama, Naohiko Aihara, Takashi Kurita, Shiro Kamakura, Wataru Shimizu

Makimoto and colleagues studied the prevalence and the clinical significance of ST-segment elevation during recovery from exercise testing in patients with Brugada syndrome (BrS). Augmentation of ST-segment elevation ≥0.05 mV in V_1 to V_3 leads compared with baseline was observed at 1 to 4 min into recovery in 37% of BrS patients and no control subjects. During follow-up, ventricular fibrillation occurred in 44% of the BrS patients with ST-segment elevation compared with only 17% in those without ST augmentation. Augmentation of ST-segment elevation during recovery from exercise testing identifies BrS patients with poor prognosis; it is thought to reflect either increased parasympathetic activity during this period or an abnormal cardiac response to this increased activity.

Editorial Comment: Sami Viskin, Raphael Rosso, p. 1585

HEART RHYTHM DISORDERS

Success of Catheter Ablation of IART in Adults With CHD 1589

Sing-Chien Yap, Louise Harris, Candice K. Silversides, Eugene Downar, Vijay S. Chauhan

Yap and colleagues investigated the acute and long-term outcome of radiofrequency catheter ablation (RFCA) for intra-atrial re-entrant tachycardia (IART) in adults with congenital heart disease (CHD). A total of 193 procedures were performed in 130 patients; 69% were initially successful. The use of electroanatomic mapping improved the likelihood of success, whereas previous Fontan palliation or Mustard repair made success less likely. IART recurrence was noted in 48% of patients over a median of 4 years. In this population of adults with CHD, a previous history of complex atrial surgery reduces the likelihood of success of RFCA for IART.